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(54) Title: COMPOSITION FOR ORAL ADMINISTRATION OF PEPTIDES

(57) Abstract

A solid pharmaceutical composition for oral administration of small and medium size peptides, particularly vasopressin, oxytocin, and their analogues, comprises said peptide, a protease inhibitor, an enteric coat and a pharmaceutically acceptable carrier containing a buffering agent buffering at a pH of from 3 to 6, preferably about pH 5. A method of manufacture of single doses of said eptide comprises mixing of the ingredients, forming the resulting mixture into spheres smaller than 2 mm, coating the spheres with an enteric coat which is readily soluble in gastric juice of pH 5.0 or higher but not at substantially lower pH, and filling the coated spheres in capsules or incorporating them into tablets, degradable in the stomach. Also disclosed is a method for oral administration to a patient of said single dose.

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COMPOSITION FOR ORAL ADMINISTRATION OF PEPTIDES

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions in solid form for oral administration of small and medium size peptides, particularly vasopressin, oxytocin, and their analogues. The present invention also relates to a method for manufacture of a single dose of said composition for oral administration of small and medium-size peptides, particularly vasopressin, oxytocin, and their analogues.

The invention further relates to a method for administration of said composition to a patient.

BACKGROUND

A number of medicines for treatment of a variety of diseases contain, as active principle, naturally occurring peptides or their synthetic analogues.

Saffran et al. (Can. J. Biochem. 57 (1979) 548-522) described a Sprague Dawley rat model for the study of the oral administration of peptide hormones. Urine retention after gastric administration of an aqueous solution of the vasopressin analog (1-deamino-4-valine)-8-D-arginine-vasopressin was found to be moderately enhanced in the presence of aprotinin.

Similarly, EP-A2 127 535, EP-A2 130 779, EP-A2 507 573, and J. Controlled Release 23 (1993) 56-74 (R.S. Geary and H.W. Schlameus), disclose the use of peptidase inhibitors as ingredients in solid pharmaceutical compositions containing biologically active peptides and their analogues. The aforementioned compositions, EP-A2 127 535, EP-A2 130 779, EP-A2 507 573, J. Controlled Release 23 (1993) 65-74 (R.S. Geary and H.W. Schlameus) have been designed, by providing them with an appropriate enteric coat, for release of their active ingredients in the small intestine, where some peptides,

particularly insulin, are known to be better absorbed.

Because of the instability of small and medium size peptides, particularly vasopressin, oxytocin, and their analogues, in the environment of the gastrointestinal tract their uptake, when given as a medicine or for similar reasons, is still very unsatisfactory. Thus, better delivery systems for non-parenteral, particularly for oral, administration of peptides and their analogues are desirable, cf. Davies, S.: "Developing delivery systems for peptides and proteins", Scrip Magazine 1992, 34-38.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide a pharmaceutical composition of the kind known in the art and mentioned above which provides for better absorption of said small or medium-size peptides, particularly vasopressin, oxytocin, and their analogues.

It is another object of the present invention to provide a method of manufacture of a single dose of said pharmaceutical composition for oral administration of small and medium-size peptides, particularly vasopressin, oxytocin, and their analogues.

It is a further object of the invention to provide a method of administration of said composition to a patient.

Additional objects of the present invention will become evident by study of the detailed description of preferred embodiments of the invention.

SUMMARY OF THE INVENTION

The above and other objects of the invention are provided by a pharmaceutical composition of the kind described above, said

composition comprising a small and medium siz peptide, particularly vasopressin, oxytocin, or an analog of vasopressin or oxytocin, a protease inhibitor, an enteric coat, and a pharmaceutically acceptable carrier containing a buffering agent buffering at a pH of from 3 to 6, preferably at about pH 5.

It is preferred for the protease inhibitor to be natural or structurally modified aprotinin. Other specific and unspecific protease inhibitors may be used; it is also possible to use mixtures of protease inhibitors. The expert will select the protease inhibitor(s), particularly serine protease inhibitors, suitable for protecting the respective peptide in the particular gastrointestinal environment. Besides native aprotinin isolated from natural sources, such as, for instance, native bovine aprotinin isolated from bovine lungs or pancreas, useful serine proteinase inhibitors comprise aprotinin and aprotinin analogues encoded by synthetic genes expressed in, e.g., yeast (Norris, K. et al., Biol. Chem. Hoppe-Seyler 371 (1990) 37-42) and E. coli (Brinkmann, T. and Tschesche, H. ibid. 43-52), and chymostatin.

It is preferred for the peptide to be chosen from DDAVP (desmopressin), oxytocin, atosiban, and carbetocin. Particularly preferred is DDAVP. For full sequences of these peptides, see Table 1 at the end of the DETAILED DESCPRIPTION section. Another group of peptides preferred for oral administration by incorporation into the composition according to the invention comprises GnRH-analogues (gonadotropin-releasing hormone analogues) such as gonadorelin and triptorelin.

It is preferred for the the pharmaceutically acceptable carrier to further comprise one or several agents selected from the group consisting of carbohydrates and modified carbohydrates and derivatives thereof, polyethylene and/or polypropylene glycol and derivativ s thereof, inorganic fillers or lubricating agents, fatty acids and th ir esters and salts,

preservatives and coating agents. Suitable pharmaceutical acceptable carriers comprise a wide variety of carriers for production of pharmaceutical formulations in tablet or capsule form, e.g. the carrier of the antidiuretic composition containing DDAVP disclosed in the European patent no. 163 723. Especially preferred are multiparticle systems, such as systems for administration in soft and hard gelatine capsules; preferred particle sizes for spheres containing peptide and/or protease inhibitor are below about 2 mm.

According to a preferred aspect of the invention the enteric coat is designed for release of its contents in the small intestine. It is particularly preferred for the particles contained in the tablets or capsules to be coated with an enteric coating for delayed release of their contents in the upper part of the small intestine. Especially preferred is delayed release of the peptide and the protease inhibitor in the duodenum and the jejunum, particularly in the duodenum and the upper jejunum. The enteric-coated spheres may also be contained in a tablet that readily disintegrates in the stomach or may be administered in suspended form in media that will not readily dissolve the enteric coating. It is also possible for the peptide and the protease inhibitor to be contained in separate spheres having the same type of enteric coating.

It is preferred for the enteric coat to be soluble in gastric juice at a pH of about 5.0 or higher; particularly preferred is a pH of about 5.5 or higher. Enteric coatings that are not readily dissolvable in such fluids at a pH of about 6.5, however, will not permit substantial release of the ingredients of the composition according to the invention in the upper small intestine and, therefore, are not preferred; on the other hand, coatings that dissolve in gastric fluids at a pH substantially lower than 5,0 are less preferred since they will release the ingredients in the stomach. Useful enteric coatings according to the inv ntion comprise polymer having dissociabl carboxylic groups, such as derivatives of cellulose, including

hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate and cellulose acetate trimellitate and similar derivatives of cellulose and other carbohydrate polymers, as well as polyvinylacetate phthalates and similar partial esters of dibasic or tribasic carboxylic acids with polyvinylacetate and similar polymers carrying alcoholic hydroxyl groups. The enteric coating may also advantageously be prepared from mixtures of such polymers.

The peptide and/or the protease inhibitor is preferably admixed with a carrier comprising a buffering agent and one or several agents selected from the group consisting of carbohydrates and modified carbohydrates and derivatives thereof, polyethylene and/or polypropylene glycol and derivatives thereof, organic and inorganic core, filler or lubricating materials, fatty acids, their esters and salts, preservatives, antioxidants, and coating agents. The buffering agent should be able to buffer at a pH from about 3 to about 6, preferably at about pH 5,5, i.e. to exert substantial buffer capacity within this range and preferably at about pH 5,5. Since the composition according to the invention is intended for preferred release in the upper part of the small intestine where, during their passage, the acidic contents of the stomach are neutralized by influx of Na^+, buffering inhibits or delays an increase of pH exceeding the preferred range or, in other words, in the direction of the upper limit of the preferred range and exceeding its upper limit. Preferred buffering agents are hydrogen and dihydrogen phosphates, such as sodium dihydrogen phosphate and mixtures of sodium dihydrogen phosphate with disodium hydrogen phosphate, calcium tetrahydrogen phosphate, citric acid and mixtures of citric acid and its monosodium salt, fumaric acid and its monosodium salt, adipic acid and its monosodium salt, tartaric acid and its sodium salt, ascorbic acid and its monosodium salt, glutamic acid, aspartic acid, betaine hydrochloride, hydrochlorides of amino acids, such as arginine monohydrochloride and glutamic acid hydrochloride, and saccharic acid. It is preferred for the buffering agent to

comprise at least 10 % by weight, more preferred at least 25 % by weight, most preferred at least 40 % by weight of the composition according to the invention. A mixture of two or more buffering constituents can be used.

According to the invention there is also provided a method of manufacture of single doses of the composition according to the invention, said method comprising the following steps:

- mixing the peptide, the proteinase inhibitor and a suitable carrier including a buffering agent buffering in the range from pH 3 to pH 6, preferably at about pH 5,
- spheronizing the mixture for formation of spheres with a diameter smaller than about 2 mm,
- coating the spheres with an enteric coat which is readily soluble in gastric juice of pH 5.0 or higher but not readily soluble at substantially lower pH,
- filling the coated spheres in capsules or incorporating them into tablets, said capsules or tablets being readily disintegrable in the stomach.

The invention further relates to a method for administration of a single dose of a small and medium-size peptide, particularly vasopressin, oxytocin, and their analogues, to a patient, comprising administering orally to the patient a tablet or capsule containing a pharmacologically effective amount of said small and medium-size peptide in form of the composition according to the invention, said tablet or capsule being disintegrable in the stomach.

DETAILED DESCRIPTION

The invention will now be described in greater detail by reference to degradation of DDAVP in gastric juice.

Example 1

Human gastro-intestinal juice was obtained from healthy male volunteers who had been fasting for 8 h. A tube was introduced intranasally after local anaesthesia with xylocaine, and gastric juice was collected. Thereafter one standardized meal was given 1 h before sampling of duodenal and distal jejunum juice and another the next morning before the collection of distal ileal juice. After centrifugation the gastric and intestinal juices were frozen in aliquots of 1 ml and stored at - 20° C.

Degradation method. The peptide or peptide analog (10 µl of 10 mM peptide in 0.9 % aqueous NaCl) was added to 190 µl of undiluted juice at 37° C. Aliquots of 25 µl were withdrawn at intervals and mixed with 100 µl acetone to stop the reaction. After centrifugation for 10 min at 10,000 g, 10 µl of the supernatant was analyzed by reversed phase HPLC. The effects of increasing amounts of aprotinin were examined under the above conditions in intestinal juice from the ileum.

Determination of peptide degradation. Analysis was carried out in a Varian 5000 HPLC analyzer equipped with a UV-detector (220 nm). Column Bondapak TM C18 (3.9 x 300 mm), eluant MeOH/0.025 M NH_4Ac (isocratic conditions), flow rate 1 ml/min.

Protein and pH determination. Protein: Bio-Rad protein assay. pH: Orion model SA720; pH-paper Merck (Darmstadt), range 4.0 - 7.0.

Results. DDAVP was found to be degraded (to about 50 % after 35 min) by both gastric and intestinal juices at pH 6.5. When the pH was adjusted to 4.0 DDAVP appeared to be essentially stable. A concentration-dependent inhibition was observed in the presence of aprotinin at pH 6.5. Absent pH-adjustment, DDAVP proteolysis was found to be slower in jejunal or duodenal juice than in ileal juice. The surprisingly pronounced in-vitro activity of aprotinin translates into more active peptide being

available for uptake by the intestinal wall.

Example 2

Experiments with healthy volunteers. After having fasted for 8 hours six healthy male volunteers were intubated (cf. example 1) with quadruple lumen flexible PVC tubes. The open end of the tube was positioned in the duodenum close to the pylorus; correct positioning was verified fluoroscopically. DDAVP acetate (0.4 mg in 2 ml 0.9 % aqueous sodium chloride was applied at the start and the tube was rinsed with 2 ml 0.9 % aqueous sodium chloride. Perfusion with aprotinin (Antagosan™, Hoechst, Germany; aqueous solution, 10,000 kallikrein inactivator units/ml) started immediately after application of DDAVP and continued for 4 h at a rate of 5 ml/min). A standard breakfast was given 5-10 min after application of DDAVP, and a standardized meal 4 h later. From 2 h after start onwards the volunteers were given 100 ml/h water orally. Each volunteer participated in three sessions.

Blood samples were drawn into EDTA K Vacutainer™ tubes, cooled immediately and centrifuged at 4° C for determination of the plasma concentration of unchanged DDAVP immediately before and, at intervals, up to 8 h after drug application, and analyzed by RIA.

Bioavailability was determined for each subject in a separate session by intravenous bolus injection of DDAVP (4 µg); blood samples were drawn before and up to 8 h after drug application and analyzed for DDAVP as described above.

For each of the volunteers DDAVP absorption in presence of aprotinin was found to increase about five-fold, i.e. from about 0.1 % by weight to about 0.5 % by weight, whereas the rate of absorption remained essentially constant. This suggests that the increased uptake is due to protection of DDAVP against proteolysis by gastric enzymes.

Exampl 3

Tablets according to the invention containing sel cted amounts of DDAVP and aprotinin can be manufactured by slight modification (addition of aprotinin) of the method disclosed in EP-A-0 163 723. These tablets can be spray-coated with useful enteric coatings such as described by Agyilirah, G. A. and Banker, G. S. in Polymers for controlled drug delivery, Tarcha, P. J., Ed., CRC Press, Boca Raton 1991, p. 39-66.

Example 4

Hard gelatin capsules containing a particulate enteric-coated DDAVP formulation according to the invention can be obtained in the following way. Solid core particles (100 g) prepared according to EP-A2-0 366 722 (example 3) are coated with 760 ml of an aqueous solution containing 20.0 mg DDAVP acetate and $7 \cdot 10^5$ kallikrein-inhibiting units of bovine aprotinin (Antagosan®; Hoechst, Germany), and these coated particles are spray-coated in a Spheronizer® fluid-bed coater with a methanol - methylene chloride 1 : 1 coating solution containing (by weight) 10 % of polyvinyl acetate phthalate (PVAP; TD-17, Colorcon Inc., West Point, PA), 0.7 of glyceryl triacetate and 1 % of stearic acid, and dried. Hard gelatin capsules are filled with these enteric-coated particles (250 mg/capsule).

Table 1

Peptide or peptide analog	Sequence
atosiban	Mpa-D-Tyr(Et)-Ile-Thr-Asn-Cys-Pro-Orn-$GlyNH_2$
carbetocin	Bua-Tyr(Me)-Ile-Gln-Asn-Cys-Pro-Leu-$GlyNH_2$
DDAVP (desmopressin)	Mpa-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-$GlyNH_2$
oxytocin	Cys-Tyr-Ile-Asn-Cys-Pro-Leu-$GlyNH_2$

Claims

1. A pharmaceutical composition in solid form for oral administration of small and medium size peptides, particularly vasopressin, oxytocin, and their analogues, said composition comprising a small and medium size peptide, particularly vasopressin, oxytocin or an analog of vasopressin or oxytocin, a protease inhibitor, an enteric coat, and a pharmaceutically acceptable carrier containing a buffering agent buffering at a pH of from 3 to 6, preferably at about pH 5.

2. The composition of claim 1, wherein the protease inhibitor is natural or structurally modified aprotinin.

3. The composition of claim 1, wherein the peptide is chosen from the group consisting of DDAVP (desmopressin), oxytocin, atosiban, and carbetocin.

4. The composition of claim 3, wherein the peptide is DDAVP.

5. Composition according to claim 1, wherein the pharmaceutically acceptable carrier further comprises one or several agents selected from the group consisting of carbohydrates and modified carbohydrates and derivatives thereof, polyethylene and/or polypropylene glycol and derivatives thereof, inorganic fillers or lubricating agents, fatty acids and their esters and salts, preservatives and coating agents.

6. Composition according to claim 1, comprising an enteric coat for release of its contents in the upper part of the small intestine.

7. Composition according to claim 6, wherein said coat is d signed for release in the duodenum and the jejunum.

8. Composition according to claim 6, wherein said coat is readily soluble in gastric juice at and above a pH of about 5.0 but not readily soluble at a substantially lower pH.

9. Composition according to claim 6, wherein said coat is readily soluble in gastric juice and at above a pH of about 5.5 but not readily soluble at a substantially lower pH.

10. Method for manufacture of single doses of the composition according to any of claims 1 to 9, comprising the following steps:

- mixing the peptide, the proteinase inhibitor and a suitable carrier including a buffering agent,
- spheronizing the mixture for formation of spheres with a diameter smaller than about 2 mm,
- coating the spheres with an enteric coat which is readily soluble in gastric juice of pH 5.0 or higher but not readily soluble at a substantially lower pH,
- filling the coated spheres in capsules or incorporating them into tablets, said capsules or tablets being readily disintegrable in the stomach.

11. A method for administration of a single dose of a small and medium-size peptide, particularly vasopressin, oxytocin, and their analogues, to a patient, comprising administering orally to the patient a tablet or capsule containing a pharmaceutically effective amount of said small and medium-size peptide in form of the composition according to the invention, said tablet or capsule being readily disintegrable in the stomach.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00244

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 37/64, A61K 37/34, A61K 45/08, A61K 47/42
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, CHEMICAL ABSTRACTS, EMBASE, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A2, 0130779 (KOWA COMPANY LTD.), 9 January 1985 (09.01.85) --	1-10
X	EP, A2, 0507573 (SANWA KAGAKU KENKYUSHO), 7 October 1992 (07.10.92), see example II-1 --	1-10
X	US, A, 5120710 (RAINER K. LIEDTKE), 9 June 1992 (09.06.92) --	1-10
X	EP, A2, 0127535 (HADASSAH MEDICAL ORGANIZATION), 5 December 1984 (05.12.84) --	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 June 1994	06 -07- 1994
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00244

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Meth Find Exp Clin Pharmacol, V lume 14, No 3, 1992, M.E.K. Kraeling et al, "Development of a colonic release capsule dosage form and the absorption of insulin" page 199 - page 209	1-10
X,P	US, A, 5206219 (ASHOK J. DESAI), 27 April 1993 (27.04.93)	1-10
A	Canadian journal of biochemistry, Volume 57, 1979, Murray Saffran et al, "A model for the study of the oral administration of peptide hormones" page 548 - page 553	1-10
A	Journal of Controlled Release, Volume 23, 1993, Richard S. Geary et al, "Vancomycin and insulin used as models for oral delivery of peptides" page 65 - page 74	1-10
A	Gen. Pharmac., Volume 23, No 1, 1992, A. N. Elias et al, "Effective portal insulin delivery with enzyme-protected capsules in pancreatectomized pigs" page 55 - page 59	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00244

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect f certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark n Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/05/94

International application No.
PCT/SE 94/00244

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0130779	09/01/85	CA-A- 1209906	19/08/86
		JP-A- 60008225	17/01/85
		US-A- 4639435	27/01/87
		US-A- 4755383	05/07/88
EP-A2- 0507573	07/10/92	JP-A- 4364131	16/12/92
US-A- 5120710	09/06/92	DE-A- 3919982	20/12/90
		EP-A- 0403748	27/12/90
EP-A2- 0127535	05/12/84	SE-T3- 0127535	
		CA-A- 1223200	23/06/87
		JP-A- 60069028	19/04/85
		US-A- 4579730	01/04/86
US-A- 5206219	27/04/93	NONE	